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Health and Environmental Effects Profile for Captan

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16. ABSTRACT

The Health and Environmental Effects Profile for captan was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Captan has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for captan is 1.0×10^{-2} (mg/kg bw/day)$^{-1}$ for oral exposure.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CAPTAN

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

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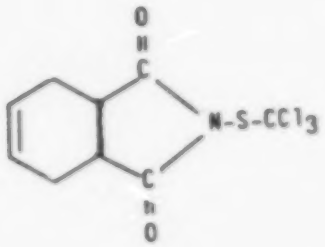
LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MATC	Maximum acceptable toxicant concentrations
ppb	Parts per billion
ppm	Parts per million
SCE	Sister chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Captan is the common name for N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide. Among its other synonyms are: N-trichloromethylthio-4-cyclohexene-1,2-dicarboxylic acid imide; 3a,4,7,7a-tetrahydro-N-trichloromethanesulphenyl-phthalimide; and 3a,4,7,7a-tetrahydro-2-(trichloromethyl)-thio-1H-isoindole-1,3(2H)-dione (BCPC, 1977). The chemical is also known by the trade names Merpan, Orthocide, Vondcaptan, Vancide-89 and SR-406 (Federal Register, 1980a). The compound has a molecular formula of $C_9H_8Cl_3NO_2S$ and a molecular weight of 300.6. Its molecular structure is shown below:



The Chemical Abstracts Service (CAS) Registry number for this compound is 133-06-2.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

In pure form, captan is an odorless, white crystalline substance. The technical grade material is a pungent, yellow to buff, amorphous powder of

90-95% purity (BCPC, 1977). Some of the physical properties of pure captan are shown below (BCPC, 1977, unless otherwise stated):

Melting Point:	178°C
Vapor Pressure at 25°C:	$<1 \times 10^{-5}$ mm Hg
Water Solubility at 20°C:	<0.5 mg/ℓ (Verschueren, 1983)
Specific Gravity (temperature unspecified):	1.73 (Federal Register, 1980a)
Henry's law constant at 25°C: (calculated)	$>4.7 \times 10^{-9}$ atmos./m^3/$mole^{-1}$ (U.S. EPA, 1981)
Log octanol/water partition coefficient:	2.35 (Verschueren, 1983; Hansch and Leo, 1981) 2.54 (Briggs, 1981)
Log soil/water distribution coefficient standardized for soil organic matter content (log K_{OC}):	2.06 (Briggs, 1981)
Soil retention factor (R_f):	0.39 (Dragun and Helling, 1981)

Chemically, captan is reasonably stable except under alkaline conditions (BCPC, 1977). Of the three different functional groups, trichloromethyl, sulfenimide and carboxyl, the two former groups are more likely to undergo hydrolysis (Wolfe et al., 1976a). Other relevant chemical reactions of environmental significance are discussed in Chapter 2.

1.3. PRODUCTION DATA

Captan is produced by the reaction of trichloromethanesulphenyl chloride on tetrahydrophthalimide, the latter being prepared by the action of ammonia on the condensation product of maleic anhydride and butadiene (BCPC, 1977). According to TSCA inventory (U.S. EPA, 1980a), only one company manufactured this chemical during the period 1975-1978. The estimated annual production of captan by Stauffer Chemical Co., Perry, OH, during this period was between 10-50 million pounds (U.S. EPA, 1980a). A more recent publication

(SRI, 1983) also lists Chevron Chem. Co., a subsidiary of Standard Oil Co. of California, as a producer of captan as of January, 1983, at Perry, OH.

1.4. USE DATA

Captan is used as a fungicide on a wide variety of fruits, vegetables and ornamentals; on numerous plant seeds; on food crop packaging boxes; in soil preplanting treatment; on inside and outside surfaces of houses; in cosmetics and pharmaceuticals, oil based paints, lacquers, wallpaper paste, plasticizers, polyethylene, vinyl, rubber stabilizers and textiles; in combination with insecticides on food crops, seed treatments and household pets. In agricultural usage, between 8.5-9.7 million pounds of captan were used annually during 1978-1979 (Federal Register, 1980a). In non-agricultural usage, between 100,000-400,000 pounds of captan was estimated to be used annually in the United States in 1979 (Federal Register, 1980a).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Like other chemicals, the fate of captan in water will depend on its ability to undergo chemical, photochemical and biological reactions. The hydrolysis of captan in water has been studied in detail by a number of investigators (Paris and Lewis, 1973; Wolfe et al., 1976a,b). The rate of hydrolysis of captan is dependent both on temperature and pH. The hydrolysis rate increases with an increase in temperature (Paris and Lewis, 1973). The pH dependence of captan hydrolysis was shown in detail by Wolfe et al. (1976a,b). Over the pH range 2-6, the reaction is pH-independent and the rate constant k_{H_2O} is calculated to be 1.8×10^{-5} sec^{-1} at 28°C. Between pH 6 and 9, the reaction is dependent on the pH and the rate constant k_{OH} for hydrolysis is calculated to be $5.7 \times 10^{2} M^{-1} sec^{-1}$ at 28°C. The products of the hydrolysis reaction are 4-cyclohexene-1,2-dicarboximide, carbon dioxide, hydrochloric acid and sulfur. A convenient way to express the hydrolytic half-life (t 1/2) of captan was given as:

$$t\ 1/2 = 0.693 \div [k_{H_2O} + k_{OH}(OH)]$$

where (OH) is the concentration of hydroxide ions.

According to the above equation, the maximum hydrolytic half-life of captan in acidic pH is ~12 hours. At pH 10, the hydrolytic half-life is ~10 seconds. At pH 7, the hydrolytic half-life at 28°C can be calculated to be ~155 minutes. With natural water from the Tombigbee River, SC, it was experimentally determined that the hydrolytic half-life of captan was 170 minutes (Wolfe et al., 1976a,b).

Direct photolysis of captan by light that was 80 times more intense than sunlight was studied by Wolfe et al. (1976b). These authors concluded that direct photolysis is unimportant in determining the fate of captan in water. However, photosensitized oxygenation of captan may be important.

Wolfe et al. (1976b) found that the half-life of captan (10^{-5} M) in water at pH 5 containing 10^{-4} M methylene blue was only 45 minutes under midday summer sunlight. The hydrolytic half-life measured in a dark control was ~9 hours, indicating that photooxidation accounted for most of the degradation under sunlight. However, the photooxidation involving singlet oxygen may be quenched by humic substances present in natural water (Wolfe et al., 1976b). For example, in a highly colored natural water (pH = 4.7) from the Suwanee River, the degradation rate of captan under midday sunlight was only slightly more rapid (30% more) than in the dark. The authors concluded that hydrolysis of captan is probably the fate determining step in natural water.

Although captan may be toxic to a few microorganisms, it is also known to be biodegraded by many isolated microorganisms. For example, O'Kelley and Deason (1976) have shown that certain strains of algae can biodegrade captan. Other isolated microorganisms (e.g., Rhizoetonia salani and Huerospora crassa) also biodegrade captan (Kluge, 1969; Richmond and Somers, 1968). The possibility of biodegradation of captan in water was studied by Paris et al. (1975). These authors found only a slight increase in the degradation rate of captan in the presence of microorganisms compared to uninoculated controls at pH 5.6-8.0. Therefore, biodegradation may not be a significant fate determining process for captan in natural water.

Neither the volatility nor the particle-mediated precipitation of captan from water have been studied comprehensively. However, Lorenz et al. (1983) have shown that the steam volatility of captan is very low. Therefore, this compound is not likely to volatilize significantly from water. From the K_{oc} and K_{ow} values (see Section 1.2.), it can be predicted that the compound may be moderately removed from water through sorption by particulate matter present in the water.

The persistence of captan in soil has been studied by a number of investigators (Burchfield, 1959; Agnihotri, 1971; Griffith and Matthews, 1969). Burchfield (1959) reported that the half-life of captan is 3-4 days in thoroughly mixed moist soil. Griffith and Matthews (1969) found that captan degraded in thoroughly mixed soil with a half-life of 1-2 days. However, captan was shown to persist for days (little change after 21 days) in soil under localized application conditions (Griffith and Matthews, 1969). Agnihotri (1971) found that captan almost fully degraded in 1 week in a forest nursery soil when applied at <250 ppm.

The processes that may be responsible for the degradation of captan in soil were studied by Ogiso et al. (1976). Both hydrolysis and microbial degradation were significant fate-determining processes for captan in soil. In alluvial soil, hydrolysis played a major role in the decomposition of captan, whereas in diluvial soil both microbial degradation and hydrolysis had significant effects on the decomposition of captan (Ogiso et al., 1976).

Due to its low vapor pressure, captan did not volatilize to any great extent in a diffusion chamber (Latham and Linn, 1965). Therefore, the disappearance of parent captan from soil through volatilization is probably not a significant process.

When ^{14}C-captan was applied to a terrestrial model ecosystem, 73% of the applied radioactivity was lost to volatilization (Gile and Gillett, 1979). The 73% included the amount of ^{14}C trapped on filters plus the estimated loss as $^{14}CO_2$. The proportions were not specified. Captan had been labeled with ^{14}C in the $-SCH_3Cl_3$ group; the determination of the fate of cyclohexene-1,2-dicarboximide moiety would require labeling of the ring. In a similar terrestrial model, 87% of the applied ^{14}C derived

from ^{14}C-captan was lost to volatilization; again captan had been labeled in the $-SCH_3Cl_3$ group (Cole and Metcalf, 1977; Metcalf et al., 1979). Dragun and Helling (1981) determined that the soil retention factor of captan with Hagerstown silty clay loam soil is 0.39. Therefore, this compound should not be very mobile in soil. In the terrestrial model ecosystem, Gile and Gillett (1979) found that 13% of the applied radioactivity from ^{14}C-captan was distributed in the soil, and only 0.01% of the radioactivity migrated to groundwater by 45 days postplanting.

Information on the fate of captan in the atmosphere was not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

3. EXPOSURE

3.1. WATER

Maddy et al. (1982) monitored 54 municipal and private wells near known high pesticide use areas in San Joaquin, Merced, Fresno, Santo Barbara and Kern counties in California and failed to detect captan in any of the well waters at a detectable limit of 5.0 ppb. Data retrieved (August 1, 1983) from STORET indicate that 183 samples consisting mostly of surface water and effluent were analyzed for captan. The maximum recorded concentration was 0.04 ppb and the mean captan concentration was 0.002 ppb. No human exposure estimate for captan through consumption of drinking water can be made unless more monitoring data are available.

3.2. FOOD

Captan residues can remain on a variety of fruits and vegetables for some time after they are sprayed. For example, Shea (1972) reported captan residue levels of 6-9 ppm in apricots 42 days after treatment, 1.5-2.5 ppm in cranberries 83 days after treatment and 3.6-11.0 ppm in prunes even after dehydration following captan treatment. In table grapes grown in the vicinity of Rome, Italy, captan was detected at a maximum concentration of 1.80 ppm (Bencivenga et al., 1980). Takeshita et al. (1976) detected captan levels of 0.034 and 0.065 ppm in 2 of 10 cucumbers grown in Japan. Many authors, however, did not detect captan in fruits and vegetables. For example, Koseki et al. (1980) analyzed spinach, cabbage, cucumbers, tomatoes, apples, pears, peaches and strawberries collected from Tokyo, Japan, and could not detect captan in any of the samples (detection limits not reported). Wilkes (1979) collected strawberries from a wholesale market

in Florida and failed to detect any captan by GLC and GC/MS, although bis-(trichloromethyl)disulfide, one of the impurities present in technical grade captan, was detected.

It is obvious from the above discussion that while captan may be present in some fruits and vegetables collected from certain regions, it may not be present in the same fruits and vegetables collected from different regions. To obtain any meaningful residue levels, a large number of samples should be analyzed. The FDA analyzed 30 composite samples of oils, fats and shortening for captan and detected captan in one sample at a level of 0.178 ppm. The average captan level in all the samples was 0.006 ppm (Manske and Johnson, 1977). Similarly, 20 composite samples of fruits were analyzed by FDA and only two samples showed captan, at levels of 0.026 ppm and 0.040 ppm. The average captan level in all composite fruit samples was evaluated to be 0.003 ppm (Johnson et al., 1981). The U.S. EPA calculated the daily dietary intake of captan from the consumption of fruits and vegetables to be 0.117 mg of captan/kg bw under the worst case scenerio (Federal Register, 1980a).

3.3. AIR

No monitoring data on the levels of captan in the ambient atmosphere could be located. Stevens and Davis (1981) determined the potential respiratory exposure of captan for workers involved in potato planting. The potential respiratory exposures to captan were 0.15-1.7 mg/hour for filling dusters and 0.037-0.042 mg/hour for the complete operation of cutting and dusting. Hansen et al. (1978) estimated an average respiratory exposure to captan of 0.033 mg/hour for personnel involved in orchard spraying. Respir-

atory exposure levels of 0.8-9.4 µg/minute for mixers and 0.07-0.66 µg/minute for sprayers were determined by Oubdier et al. (1974) during orchard spraying operations.

3.4. DERMAL

Dermal exposure to captan is most prevalent in occupational settings. An average captan exposure of 1.94 mg/man/hour was calculated for personnel involved in orchard spraying (Hansen et al., 1978). The total dermal exposures to captan were 1.2-15 mg/hour for filling dusters and 0.40-0.70 mg/hour for the complete operation of cutting and dusting (Stevens and Davis, 1981). Kazen et al. (1974), however, using a hexane rinsing technique, recovered as much as 23 µg of captan on the hand of a home gardener and 570 µg on the hand of a farmer.

4. PHARMACOKINETICS

DeBaun et al. (1974) administered [trichloromethyl-^{14}C] captan (100 mg/kg average) by gavage to Simonsen albino rats (8 male and 8 female) in an aqueous suspension of 1% tragacanth gum-0.05% Tween-20. Two male rats were dosed with 20 mg/kg intraperitoneally in 0.5 mℓ of dimethyl sulphoxidecorn oil (1:6 v/v). In an initial range-finding experiment, captan was well absorbed (percent not calculated) following oral administration of doses <134 mg/kg. At a dose of 650 mg/kg, the percent of the administered radioactivity in the feces increased and unmetabolized captan was detected, indicating that part of the administered dose may not have been absorbed. At 1 day following dosing with 100 mg/kg, radioactivity was concentrated in the gastrointestinal tract, kidney and bladder (Table 4-1). By 8 days, the level of radioactivity had declined extensively, with the highest levels remaining in the lung, kidneys and bladder, organs involved in the excretion of captan metabolites. There were no significant differences in distribution between males and females. Based on the half-life for retention in the body, absorption is much more rapid following an oral dose (t 1/2 = 9 hours) than following an i.p. dose (t 1/2 = 2 days).

Metabolism of captan is thought to involve reaction with a thiol compound at the trichloro-methylthio moiety, with the evolution of thiophosgene ($CSCl_2$) (DeBaun et al., 1974). Three detoxification products of thiophosgene have been identified: dithiobis-(methanesulphonic acid) derived by reaction with sulphite; CO_2 resulting from oxidation and/or hydrolysis; and thiazolidine-2-thione-4-carboxylic acid derived from reaction with a cysteine moiety.

Following oral administration, captan is metabolized and excreted (DeBaun et al., 1974). Within 4 days of dosing, the majority of the

TABLE 4-1

Distribution of ^{14}C in Tissues and Organs of Rats Following Oral Administration of [^{14}C]Captan[a,b]

Sample	Analysis Interval			
	1-Day	2-Day	4-Day	8-Day
Bladder	6.13	3.87	1.83	1.97
Blood	2.95	2.22	1.44	0.98
Brain	1.22	0.93	0.69	0.60
Fat	0.27	0.22	0.22	0.16
Gonad	2.49	2.13	1.31	0.69
Intestine	31.17	2.31	0.62	0.22
Kidney	11.55	7.36	4.27	2.11
Liver	4.22	2.61	1.53	0.69
Lung	3.93	2.62	1.90	1.01
Muscle	1.43	1.08	1.08	0.85
Stomach	33.78	9.47	2.69	0.42
Carcass	0.66	0.39	0.32	0.22

[a]Source: DeBaun et al., 1974

[b]Values are expressed as ppm of captan equivalents. All represent averages of residues from two male and two female rats administered [^{14}C]captan at a dose of 100 mg/kg bw.

administered radioactivity had been recovered in the urine, feces and expired air (51.8, 15.9 and 22.8%, respectively). Only 0.6% of the dose remained in the tissues; however, 8.9% was not accounted for.

Peeples and Dalvi (1978) studied the metabolism of captan by male Sprague-Dawley rats and by hepatic microsomes. Oral administration of 650 mg/kg bw resulted in decreased P-450 activity 24 hours after dosing. Pretreatment with diethyl maleate, a depletor of cellular sulfhydral groups, increased the magnitude of the observed decrease. In vitro, captan inhibited the activity of benzphetamine N-demethylase and aniline hydroxylase and decreased the concentration of cytochrome P-450. Metabolism was observed to proceed through the formation of thiophosgene.

Couch et al. (1977) investigated the excretion and distribution of [^{35}S] captan in male Sprague-Dawley rats following single or multiple i.p. injections of 6 mg/kg bw in corn oil to intact or partially hepatectomized animals. After 72 hours, 76% of the administered radioactivity was recovered in the urine and 13% in the feces. No differences were observed between intact and 70% hepatectomized rats. Hepatic nuclei isolated from both intact and hepatectomized rats contained significant amounts of bound radioactivity (0.008-0.009 µg ^{35}S/g tissue). Fractionation of the nuclei revealed a distribution of nuclear sap protein (10%), deoxyribonucleoprotein (including histones) (14%), "residual" protein (16%) and acidic ribonucleoprotein (39%).

5. EFFECTS

5.1. CARCINOGENICITY

Captan has been tested for carcinogenicity in Osborne-Mendel rats and B6C3F1 mice by the National Cancer Institute (NCI, 1977). Maximum tolerated concentration for both species of 16,000 ppm captan in the diet were determined in preliminary subchronic studies using groups of five male and five female animals/species. Concentrations ranged from 500-32,000 ppm in the feed, administered for 6 weeks followed by 2 weeks of observation. Concentrations of 8000 and 16,000 ppm were chosen for both species for the chronic studies because there were no deaths at either of these dose levels during the subchronic study and because the animals adapted to the captan so that weight gains, while initially depressed at 16,000 ppm (both species) and 8000 ppm (rats only), approached those of the controls by the end of the subchronic study. In the chronic study, treated groups were composed of 50 animals of each sex for each species. The matched control groups consisted of only 10 animals of each sex/species, so pooled controls were used for statistical analyses.

A dietary concentration of 16,000 ppm proved to be highly toxic to rats in the chronic study and these groups were terminated after 18 weeks. The groups receiving 8000 ppm were redesignated as the "high-dose," and additional groups of rats were started at a dose of 4000 ppm, 20 weeks after the beginning of the study. At this time, seven males and one female that had died in the 8000 ppm groups were replaced by healthy animals from the 16,000 ppm group. Later in the study, the dietary levels of captan for both groups were halved. The resulting TWA dietary levels for the 80 weeks of treatment were 2525 ppm for the low-dose group and 6050 ppm for the high-dose group. The treatment period was followed by an observation period of 33-34 weeks.

No dose-related tumors were observed in male rats. A positive dose-related trend was observed in female rats for adrenal cortical tumors (0, 4 and 6% for pooled controls, low- and high-dose, respectively ($p=0.047$ using Cochran-Armitage test) and C-cell adenoma of the thyroid (1.5, 2 and 9% for pooled controls, low- and high-dose, respectively, $p=0.035$). However, the Fisher exact test demonstrated no significant differences in tumor incidence between control and treatment groups. Since these types of tumors often arise spontaneously in female rats, it was concluded that none of the tumors observed could be related to captan treatment.

Mice were administered 8000 or 16,000 ppm captan in the diet for 80 weeks followed by 11 weeks of observation. The incidences of polypoid carcinoma (i.e., adenocarcinoma in adenomatous polyp) of the duodenum showed a statistically significant ($p<0.05$ using Cochran-Armitage test), positive, dose-related trend in both males (pooled controls 0/68, low-dose 1/43, high-dose 3/46) and females (pooled controls 0/68, low-dose 0/49, high-dose 3/48), although incidences in treated groups were not statistically significantly different from controls when analyzed by the Fisher exact test. When data for combined incidences of polypoid carcinoma and adenomatous polyp (not otherwise specified) of the duodenum in male mice were analyzed, the incidence for the high-dose group was significantly higher than controls by the Fisher exact test [pooled controls 0/68, low-dose 3/43, high-dose 5/46 ($p=0.009$)]. Combining the incidences of these tumors for female mice did not result in statistical significance by the Fisher exact test.

Duodenal lesions are usually rare in mice, so their occurrence in both sexes was considered significant. The authors concluded that "under the conditions of this bioassay, tumors in the duodenum of B6C3F1 mice were

associated with treatment with captan, but there was no convincing evidence that the tumors observed in Osborne-Mendel rats were related to treatment."

In another study, groups of 18 male and 18 female mice of two hybrid strains, B6C3F1 and B6AKF1, were treated with captan in gelatin at gavage doses of 215 mg/kg bw/day (the maximum tolerated dose, which was determined from the average body weight of young mice and not corrected for weight gain) from day 7 to day 28 of age. After day 28, captan was given in the diet at a level of 560 ppm for ~18 months (BRL, 1968; Innes et al., 1969). Negative controls consisted of untreated and vehicle treated mice of both sexes of both strains. At the end of the treatment period, the mice were killed and examined for gross pathological lesions. Histologic examination was performed on all major organs and gross lesions. There was no observed increased incidence of tumors in either sex of either strain above controls.

Captan in gelatin was administered subcutaneously to groups of 18 male and 18 female mice of two hybrid strains, B6C3F1 and B6AKF1 as a single dose of 1000 mg/kg bw on day 28 of life (BRL, 1968). The mice were observed for ~74 weeks. Controls consisted of similar groups of untreated or vehicle treated mice. There was no increased incidence of tumors in the surviving mice (15-17/group) killed at the end of the observation period when compared with controls.

Previous unpublished studies (Weir, 1956; Reyna et al., 1973a) have failed to detect any statistically significant increase in tumor incidence in rats fed diets containing up to 5000 ppm captan for 2 years (Weir, 1956; Reyna et al., 1973a) or in mice fed diets containing up to 7500 ppm for 18 months (Reyna et al., 1973b). These studies are of limited significance, since the Weir study had only 10 rats/group and the studies by Reyna et al. (1973a,b), performed at Industrial Bio-Test, were judged to be invalid (Federal Register, 1980a).

5.2. MUTAGENICITY

Captan has been tested extensively for mutagenicity in bacterial test systems (Table 5-1). Dose-related responses in these tests have consistently indicated captan to be a mutagen in the absence of mammalian activating systems. Inclusion of an activating system, such as rat liver S-9, results in a significant decrease in mutagenic potency (Shiau et al., 1981; Herbold and Buselmair, 1976).

Host-mediated and fluid-mediated assays have yielded negative results for captan in bacteria (Ficsor et al., 1978; Kennedy et al., 1975a; reviewed by Legator et al., 1982). Ficsor et al. (1978) performed host-mediated and body fluid-mediated assays with Sprague-Dawley rats or Swiss albino mice using Salmonella typhimurium strains his G46, TA1950 and TA100. Negative results were obtained in the host-mediated assay with his G46 in mice treated subcutaneously with 1500 mg/kg or orally with 1000 mg/kg of captan and with TA1950 in rats treated orally with 2000 mg/kg of captan. Negative results were also obtained with his G46 in spot tests using blood or urine from mice treated orally with 250 mg/kg of captan and with a TA1950 culture incubated with an equal volume of blood from rats treated orally with 2000 mg/kg or intraperitoneally with 500 mg/kg of captan. In in vitro experiments, both rat blood and human blood were found to inactivate 500-1000 µg captan/ml; however, rat plasma inactivated ~10 times less captan than did rat blood. It was concluded that captan was probably inactivated by reaction with glutathione in the erythrocytes. Negative results were also obtained by Kennedy et al. (1975a) with S. typhimurium his G46 in the host-mediated assay in rats treated orally with 125 or 250 mg captan/kg/day for 14 days.

Strobel and Greb (1981) obtained positive results in a cell transformation assay using BHK21C13 cells in the presence of mouse S-9 mix. An

TABLE 5-1

Mutagenicity of Captan in Bacterial Systems

Assay	Indicator Organism	Strain	Concentration or Dose	Application Method	Activation System	Response	Comments	Reference
Reverse mutation	S. typhimurium	TA1535 TA1537 TA1538 TA98 TA100	<10 mg/plate	plate incorporation	+/-	+	Responses were not reported individually for each strain or for the presence or absence of S-9.	Waters et al., 1982
Reverse mutation	S. typhimurium	TA100 TA98 TA1535 TA1537 TA1538	100 µg/plate	plate incorporation	+/-	+	Although revertant colonies were produced regardless of the presence or absence of of an activating system, many more revertant colonies were produced in the absence of S-9.	Moriya et al., 1983
Reverse mutation	S. typhimurium	TA1535 TA1536 TA1537 TA1538	50 µg/plate	plate incorporation	NR	+ - - -	NC	Shirasu et al., 1976, Kada et al., 1974
Reverse mutation	S. typhimurium	TA1535 TA1536 TA1537 TA1538 TA98 TA100	50, 100 or 300 µg/plate	spot test	+/-	-/- -/+	The only positive response was observed in strain TA100 in the absence of S-9.	Shiau et al., 1981
Reverse mutation	S. typhimurium	TA100 TA1535	8 µg/plate	plate incorporation	-	+	Preincubation in acidic media, with or without gastric juices, increased the number of revertant colonies observed after 48 hours of incubation.	Deflora and Boido, 1980
Reverse mutation	S. typhimurium	TA1535 TA1536 TA1537 TA1538 G46	1-20 mg/mt	NR	+	+	Strains TA1535 and TA1536 had increased numbers of revertant colonies at 1 mg/mt, although no revertant colonies were seen at higher exposure levels. G46 had an increased number of revertant colonies at the highest exposure level.	Herbold and Buselmaier, 1976
Reverse mutation	S. typhimurium	TA1535 TA1538	0.15 µmole/plate	plate incorporation	+/-	-/+	Incubation with cysteine or rat blood also abolished the mutagenicity of captan.	Moriya et al., 1978

TABLE 5-1 (cont.)

Assay	Indicator Organism	Strain	Concentration or Dose	Application Method	Activation System	Response	Comments	Reference
Reverse mutation	S. typhimurium	TA98 TA100	100 µg/plate	plate incorporation	+/-	+/-	NC	Wildeman and Nazar, 1982
Reverse mutation	S. typhimurium	TA100	1-300 µg/ plate	liquid incubation assay	-	-	Incubation took place for 30 minutes prior to plating.	Shiau et al., 1981
Reverse mutation	B. subtilis	TKJ5211 TKJ6321	15, 100 or 300 µg/plate	spot test	+/-	-/+	The test was positive in the absence of S-9; the authors reported what appeared to be a total increase in colony counts, rather than the presence or absence of a ring of revertant colonies.	Shiau et al., 1981
Reverse mutation	B. subtilis	TKJ5211 TKJ6321	1-300 µg/ plate	liquid incubation assay	-	+	Incubation took place for 30 minutes prior to plating.	Shiau et al., 1981
Rec assay	B. subtilis	H17 Rec$^+$ H17 Rec$^-$	20 µg/disk	spot test	NR	+	The result was positive in both strains.	Shirasu et al., 1976
Reverse mutation	E. coli	WWP-2 hcr$^+$ WWP-2 hcr$^-$	10-15 mg/plate	spot test	-	+	NC	Clarke, 1971
Reverse mutation	E. coli	WP2 try hcr$^+$ WP2 try hcr$^-$	50 µg/plate	plate incorporation	NR	+	NC	Shirasu et al., 1976; Kada et al., 1974
Reverse mutation	E. coli	WP2 hcr	NR	plate incorporation	NR	+	NC	Moriya et al., 1983
Reverse mutation	E. coli	WP2 hcr	0.15 µmole/ plate	plate incorporation	+/-	-/+	Incubation with rat blood or cysteine also abolished the mutagenicity of captan.	Moriya et al., 1978
Reverse mutation	E. coli	WP2 uvr A	<10 mg/plate	plate incorporation	+/-	+	NC	Waters et al., 1983

NR = Not reported; NA = Not available; NC = No comment

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increase in transformants per $2x10^8$ cells was observed with doses ranging from 2.5-25 µg/mℓ. No increase in the number of transformants was observed at a dose of <2 µg/mℓ.

An interesting series of experiments has been performed by Bridges et al. (1972, 1973) using DNA repair-deficient and proficient strains of Escherichia coli (WP2recA, WP2exrA, WP2uvrAexrA, WP2 and WP2uvrA). Captan was applied directly to the media (1 mg impregnated in filter paper) or as a vapor (1 mg impregnated in filter paper applied to the lid rather than the agar). These experiments demonstrated the existence of two mutagenic species. One is a diffusible mutagen, possibly captan itself, which is $exrA^+$-dependent. The other is a volatile compound, possibly produced by the hydrolysis of captan, which is $exrA^+$ and $recA^+$-independent. Captan was positive in differential toxicity assays in the E. coli strains p3478 ($polA^-$) and w3100 ($polA^+$), the B. subtilis strains M45 ($recA^-$) and H17 ($recA^+$), and S. typhimurium strains SL4700 (rec^-) and SL4525 (rec^+) (Waters et al., 1983).

Captan has been tested for mutagenicity in Chinese hamster ovary cells using induction of resistance to 6-thioguanine (O'Neill et al., 1981), and by Chinese hamster V79 cells for 8-azaguanine or ouabain (Arlett et al., 1975). In the absence of exogenous metabolic activation, O'Neill et al. (1981) observed a dose-response curve for seven concentrations between 0 and 4 µg/mℓ in three separate experiments. The lowest concentration at which a statistically significant increase in mutation frequency was observed was 0.25 µg/mℓ. Arlett et al. (1975) exposed V79-4 cells either directly to captan in the media (5 or 10 µg/mℓ) or to captan vapors (10-10,000 µg/pad). Direct exposure resulted in a slight dose-

related increase in ouabain-resistant colonies, but no increase in 8-azaguanine-resistant colonies. Exposure to captan vapor resulted in increased responses for both types of forward-mutation.

Captan has been observed to induce SCE formation in Chinese hamster V79 cells (Tezuka et al., 1980) and human lymphocytes (Vigfusson and Vyse, 1980). Tezuka et al. (1980) observed a dose-dependent increase in SCEs/cell with captan concentrations ranging from $6x10^{-6}$ M, 6.6±0.5 SCE/cell, to $6x10^{-5}$ M, 24.9±1.1 SCE/cell vs. 4.7±0.2 SCE/cell for background control. Dose-related increases in chromosomal aberrations of all types were observed at concentrations of $3x10^{-5}$ M or higher. Vigfusson and Vyse (1980) exposed human lymphocytes to captan at concentrations of $1x10^{-5}$ M, $1x10^{-4}$ M, or $1x10^{-3}$ M (3, 30 or 300 mg/ml medium). Captan was toxic at the two highest concentrations; however, a significant increase in SCEs was observed at the low dose. In this study, captan produced significantly more SCEs than did an equal concentration of ethylmethane sulfonate (EMS), a known inducer of SCE and mutation.

Captan has also given positive results in a number of tests indicative of DNA damage. Waters et al. (1983) obtained a dose-related increase of >3-fold in mitotic recombination in Saccharomyces cerevisiae D3 without metabolic activation. Painter and Howard (1982) found that a dose of $8.3x10^{-6}$ M captan would inhibit DNA-synthesis in HeLa cells in the absence of an S-9 activating system. Induction of unscheduled DNA synthesis (UDS) has been measured in SV-40 transformed human cells (Ahmed et al., 1977), in rat hepatocytes (Probst and Hill, 1980; Probst et al., 1981), and in rat thymocytes and human lymphocytes (Rocchi et al., 1980). Ahmed et al. (1977) tested captan in concentrations ranging from 1-1000 µM, both with and without activation by rat liver S-9 preparations; a statistically signifi-

cant increase in UDS was observed in SV-40 transformed human cells with all concentrations tested, in either the presence or absence of an activating system. Negative results were obtained by Probst and Hill (1980) and Probst et al. (1980) in tests utilizing rat hepatocytes. This negative result could indicate an inability of hepatocytes to activate captan or the presence of efficient detoxification systems. Rocchi et al. (1980) reported that captan produced up to 82% inhibition of scheduled DNA synthesis in rat thymocytes at a dose of 8 µg/mℓ. In human lymphocytes, a dose of 5 µg/mℓ did not induce or inhibit UDS following exposure to UV irradiation (300 ergs/mm²). Swenberg et al. (1976)) monitored DNA damage in Chinese hamster lung fibroblast (V79) cells by an *in vitro*/alkaline elution assay, with or without a rat liver S-9 activating system. In the absence of an activating system, DNA damage was detected at concentrations of 0.03, 0.1, 0.3 and 1.0 mM. In the presence of an activating system, no DNA damage was observed at concentrations as high as 3.0 mM. Captan failed to induce UDS in human lung fibroblasts (WI-38) with or without metabolic activation (Waters et al., 1983).

There has been testing involving eukaryotic systems *in vivo*. Mollet and Wuergler (1974) tested the ability of captan to induce somatic recombination, as determined by the frequency of mosaic eyes, in *Drosophila melanogaster*. Methyl methanesulphonate, a known potent mutagen, was used as a positive control in these experiments. No increase in the frequency of mosaic eyes was noted when captan was included in the media at concentrations of 0.78 or 1.45%. However, captan was positive in *D. melanogaster* when tested for gene mutations as measured by recessive lethality, eliciting a >0.2% increase in background mutation rate by the F_3 generation (Waters et al., 1983).

Dominant lethal and cytogenetic studies in mice have been reported as negative (Tezuka et al., 1978; Kennedy et al., 1975a; Fry and Ficsor, 1978), except for the dominant lethal test in CBA-J mice (Collins, 1972). Tezuka et al. (1978) dosed male C3H mice with single oral doses 500, 1000 or 2000 mg/kg or with five consecutive doses (interval between doses unspecified) of 200, 400 or 800 mg/kg/day. A cytogenetic study of the bone marrow cells from these mice revealed no chromosomal aberrations. When the males that received 5 daily doses were mated with virgin female SLC-ICR mice, no decrease in fertility or induction of dominant lethal mutations was detected as a result of captan treatment. Negative results were also obtained in the dominant lethal assay with mice by Kennedy et al. (1975a) following a single i.p. injection of 3 or 6 mg/kg and by Waters et al. (1983) in male mice treated for 7 days with captan in the diet at 0, 25, 50 and 100% of the maximum tolerated dose. The work by Kennedy et al. (1975a) performed at Industrial Bio-Test Laboratories, used a low dosage and had no controls. Additionally, the U.S. EPA (1983) has classified mouse mutagenicity experiments on captan performed at Industrial Bio-Test invalid.

Fry and Ficsor (1978) obtained negative results in cytogenetic studies of Swiss albino mouse bone marrow (2-4 mice/group) following i.p. administration of 250 mg captan/kg bw. No statistically significant increase in chromosomal abnormalities was observed at any time; however, a single metacentric chromsome was observed in each of the 6, 30 and 54 hour treatment groups (1001 metaphases observed), whereas no metacentric chromosomes were observed in 1495 metaphases from control animals.

In the dominant lethal assay, Collins (1972a) found that, using an increase in early deaths as a measure of mutation, captan given intraperitoneally for 5 days (10.0 mg/kg/day) to male CBA-J mice produced effects on

mouse spermatocytes. Oral doses (200 mg/kg/day for 5 days) affected mainly epididymal sperm and late spermatids. The author suggested that "captan may exhibit mutagenic properties when administered in repeated doses."

Captan has also been tested in the heritable translocation assay (Simmon et al., 1977; Jorgenson et al., 1978). Male mice were fed diets containing 2500 or 5000 ppm captan for 8 weeks, then bred to untreated females. Of 200 progeny examined from each dose level, only 1 animal demonstrated semisterility, which would be sufficient to classify captan as positive for heritable translocations. However, one translocation was also seen in the negative control group. This exception in the control makes it difficult to interpret the significance of the translocation found in the treated group (U.S. EPA, 1980b).

Collins (1972b) measured reproductive fitness in male DBA/2J mice as an indicator for mutation. Reproductive fitness is a polygenetic trait and should, therefore, be more sensitive than the dominant lethal assay. Captan was administered for 5 days (50 or 100 mg/kg/day) to mature males, which were bred to untreated females to obtain the F_1 generation. The F_1 animals were then bred to obtain an F_2 generation. Dose-related decreases in the average number of survivors from birth to day 4 were observed in both generations. Significant differences were observed in the average weaning weight in both generations following captan treatment of the F_0 males, implying that treatment affected the growth of the mice. Captan thus appears to be weakly mutagenic in this test.

In summary, there is evidence that captan can cause gene mutations in bacteria, mammalian cells in culture and Drosophila. Several other studies evaluating SCE formation, mitotic recombination, and UDS confirm the DNA damaging potential of captan. The presence of an exogenous activation

system is not necessary for the detection of mutagenic activity; rather, its presence has resulted in decreased mutagenic activity. It can not be ruled out that the decreased mutagenicity is simply due to nonspecific binding of captan with proteins in the activation system, rather than detoxification. The ability of captan to cause genetic damage in intact animals has not been adequately evaluated; however, positive results were obtained in the Drosophila sex-linked recessive assay. Although there have been isolated incidences of increased effects in whole rodent studies, these studies are not wholly unequivocal.

In conclusion, the weight-of-evidence indicates that captan is mutagenic as shown by studies in bacteria, yeast, mammalian cells in culture and Drosophila. Although captan is judged as a potential mammalian mutagen, additional studies are needed in intact mammals to confirm its mutagenic properties in vivo and evaluate its ability to reach and damage mammalian germ cell DNA.

5.3. TERATOGENICITY

Fabro et al. (1966) dosed New Zealand white rabbits with 80 mg captan/kg bw on days 7-12 of pregnancy. No increased incidence of resorptions, increased appearance of malformed fetuses, decreased fetal weight or decreased litter size were detected.

Kennedy et al. (1968) administered captan orally at doses of 18.75, 37.5 or 75.0 mg/kg/day to groups of 5-7 pregnant New Zealand White or Dutch Belted rabbits on days 6-18 of gestation; at doses of 50, 100, 250, 500, 1000 or 2000 mg/kg/day to groups of 5-7 pregnant Charles River rats on days 6-15 of gestation; and at doses of 125, 250, 500 or 1000 mg/kg/day to groups of 14-23 Syrian Golden hamsters on days 1-15 of gestation. No malformed fetuses were observed in any treatment group; however, the high-dose group

of New Zealand White rabbits had reduced fetal weight, reduced crown-to-rump length and an increased number of resorption sites. High doses of captan, therefore, appear to be fetotoxic to this strain of rabbit. In the rats, a slight reduction in fetal weight was observed in the high dose group; however, no dose-related malformations were noted. A significant increase in resorptions was recorded in the high-dose group for hamsters; however, this may have been related to the decreased food consumption observed with doses $\geq$250 mg/kg. Again, there was no dose-related increase in malformations.

McLaughlin et al. (1969) administered captan (37.5, 75.0 and 150.0 mg/kg bw) in gelatin capsules to New Zealand White rabbits (6-9 rabbits/group) on days 6-16 of gestation. One of 49 fetuses was malformed at a dose of 37.5 mg/kg, and 9 of 75 fetuses were malformed at a dose of 75.0 mg/kg. Malformations observed included cleft lip, fused upper lip, deformed limbs and acephaly.

In an abstract of a French paper, Alnot et al. (1974) were reported to have observed that captan was more toxic to pregnant than to non-pregnant Wistar rats. Increases in resorption nodules and ocular lesions in the survivors were reported (dose and days of treatment were not given in the abstract).

Robens (1970) administered captan (total doses of 200-2500 mg/kg) orally to 3-10 pregnant Syrian Golden hamsters on days 7, 8 or 6-10 of gestation. Multiple doses resulted predominantly in maternal mortality; however, single doses produced a number of malformations in the 272 fetuses examined, including exencephaly (13), cranial pimple (6), fused ribs (19), cleft palate or harelip (1), short or curved tail (1), limb defects (4) and umbilical hernia (1). These malformations occurred primarily among the

groups administered doses ≥600 mg/kg. Malformations among the 1081 fetuses from vehicle controls were rare: exancephaly (1), cranial pimple (1) and fused ribs (1).

Courtney et al. (1978) studied the teratogenic effects of captan administered by a variety of routes to pregnant CD-1 mice on days 6-13 of gestation. No abnormalities in term fetuses were observed following oral or subcutaneously administered doses of 100 mg captan/kg bw/day or inhalation of captan at 488 mg/m³, 4 hours/day.

Kennedy et al. (1975b) administered captan in the diet (30 or 60 mg/kg bw) to beagles (6 per group) during the entire gestation period and during an 8-week lactation period. No toxic effects were noted in the mothers at these dose levels. None of the pups in the treatment groups were malformed and no increase in resorptions was observed.

The teratogenic potential of captan in non-human primates (rhesus monkeys and stump-tailed macaques, 7/group) has been determined by Vondruska et al. (1971). Captan was administered orally as a suspension in a solution of cream of coconut at a dose of 10.0, 25.0 or 75.0 mg/kg/day on days 21-34 of gestation. No evidence for fetotoxicity or teratogenicity was obtained.

Several of the teratology studies discussed above were performed at Industrial Bio-Test Laboratories. It appears that the monkey (Vondruska et al., 1971) and the rat, rabbit and hamster (Kennedy et al., 1968) teratology studies are among the Industrial Bio-Test studies invalidated by the U.S. EPA (1983).

5.4. OTHER REPRODUCTIVE EFFECTS

No reproductive effects other than those discussed in Sections 5.2. and 5.3. were encountered in the available literature.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The best chronic toxicity data available are contained in the NCI bioassay report (NCI, 1977) (see Section 5.1.). The average body weight of the Osborne-Mendel rats was lower at both treatment levels (2525 and 6050 ppm in the diet) in both sexes than in the corresponding controls throughout the 2-year treatment; however, no statistically significant dose-related decrease in survival was observed. During the second year of the study, rough hair coats, alopecia, pale mucous membranes, dermatitis, tachypnea and hematuria were observed in both high- and low-dose groups. Vaginal bleeding was noted in a few of the treated females. A number of lesions were observed during gross and microscopic examinations of the skin, lungs, bronchi, trachea, bone, bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder, pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate, uterus, testis, ovary and brain. The lesions observed are frequently seen in rats and did not differ in frequency between treated and control groups.

A dose-related decrease in body weight was observed in both male and female B6C3F1 mice (8000 and 16,000 ppm) throughout the study. Excessive excitability and slight tremors were noted in the high-dose females at 24 weeks, but not later. Clinical signs, including rough hair coats, alopecia and abdominal distention, appeared in the treated animals after 50 weeks. Both the low- and high-dose treated males evidenced signs of excitability and abdominal distention at 71 and 80 weeks, respectively. A purulent discharge from the penis was observed in one male from each treatment group during the last 6 weeks of the study. Irritation and redness of the

perineal areas were observed in some of the high-dose males. Gross and microscopic examination of the organs revealed no compound-related lesions.

Dekanozishvili (1975) administered a total dose of 78 mg captan/kg bw orally to rats over a 2-month period. Effects were seen on blood hemoglobin concentration, leukocyte count, erythrocyte count, prothrombin levels, serum cholesterol and sperm motility. The toxic response was greater when the compound was administered intermittently rather than continuously. The abstract did not specify what was meant by an intermittent dose.

Szuperski and Grabarska (1972) administered 0.5 g captan/kg bw/day orally to rabbits for 14 days. They reported dystrophic changes in the kidneys, lungs, spleen, stomach and intestinal mucosa. Glycogen storage in the liver and muscles was inhibited, and an increased reaction to vitamin C was observed.

Vashakidze et al. (1973) administered captan by an unspecified route to rats (265 mg/kg bw/day for 2 months or 20-55 mg/kg bw/day for 12 months). Pathologic changes observed included dystrophic changes in the liver, hypochromic anemia, leukopenia and functional changes in the testes. A number of serum enzyme levels were effected, including decreased cholinesterase activity and increased alanine transaminase and aspartate transaminase activities.

5.6. OTHER RELEVANT INFORMATION

Several values have been reported for LD_{50}s or LC_{50}s (NIOSH, 1983). In the rat, the LD_{50} following oral administration is reported to be 10 g/kg bw. Values are similar in the mouse, with a reported oral LD_{50} of 7 g/kg bw; however, captan is much more potent when administered intraperitoneally (LD_{50} = 0.462 g/kg bw). An inhalation LC_{50} for mice has been reported to be 5 g/m³ with a 2-hour exposure period.

The effect of dietary protein on captan toxicity has been determined (Krijnen and Boyd, 1970; Boyd and Krijnen, 1968). LD_{50}s in male Wistar rats fed diets containing 0, 1/7, 1/3, 1 and 3 times the optimal protein concentration (26% casein) were determined to be 6.15, 480, 10,670, 12,600 and 5320 mg/kg, respectively. Time to death was a function of dose but was not affected by dietary protein concentrations. These data indicate that either protein deficient diets or excessive protein intake may increase the hazard of exposure to captan.

Marzulli and Maibach (1974) tested captan for skin sensitization in humans using the Draize test. This test consists of a 3-5 week induction period in which the subjects were exposed to a 1% solution in petrolatum of captan daily, a 2-week rest period, and a challenge with a 1% captan solution. Of the exposed subjects, 4.4% developed an immunological reaction to captan.

Captan has been demonstrated to inhibit DNA polymerases by competing with DNA for the binding site on the polymerase and irreversibly altering the polymerase (Dillwith and Lewis, 1982). The inhibition was not effected by the base sequence of the polynucleotide template, and the fidelity with which the DNA template is copied by DNA polymerase I is not altered. Lewis and Brown (1978) reported inhibition of DNA polymerizing activities in intact nuclei but the soluble DNA polymerizing activity was not inhibited.

Captan has also been found to stimulate the rate of Ca^{2+} efflux from rat liver mitochondria (Hertel et al., 1981), to induce p-nitroanisole-O-demethylase activity and benzo[a]pyrene-DNA binding in rats *in vivo* (Mikol et al., 1980) and to inhibit the *in vitro* activities of intestinal and hepatic aryl hydrocarbon hydroxylase when incubated with microsomes prepared from male rats (Stohs and Wu, 1982).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity of captan has been determined in at least 16 species of freshwater fish (Table 6-1). Brook trout, lake trout, cutthroat trout and chinook salmon were the most sensitive species tested, with 96-hour LC_{50} values ranging from 0.034-0.057 mg/ℓ (Johnson and Finley, 1980; Hermanutz et al., 1973). The harlequin fish, having 48- and 96-hour LC_{50} values of 0.33 and and 0.30, respectively, and carp, pond loach and the medaka, having 48-hour LC_{50} values of 0.25, 0.34 and 1.00 mg/ℓ, respectively, were the most resistant to captan exposure (Johnson and Finley, 1980; Spehar et al., 1982; Hermanutz et al., 1973). Van Hoof (1980) reported that captan at 0.25 and 0.50 mg/ℓ causes death in rainbow trout within 6 and 5 hours, respectively.

Zebrafish larvae, Brachydanio rerio, exposed to 1.0 mg captan/ℓ began dying after 40 minutes, and 98% died within 90 minutes (Abedi and McKinley, 1967). Captan-related injury included extensive, rapid head and eye rupturing.

Juvenile crayfish, Procambarus clarkii, were quite resistant to captan (Captan 80 WP) exposure, having a 96-hour LC_{50} of 15,631 mg/ℓ (Cheah et al., 1980).

6.2. CHRONIC EFFECTS

The effects of captan on the survival and reproduction of fathead minnows was determined during 45-week tests (Hermanutz et al., 1973). For parental fathead minnows, Pimephales promelas, survival was slightly reduced (not statistically significant) in those exposed to 0.0395 mg captan/ℓ. Of adults exposed to 0.0635 mg captan/ℓ 49 of 50 died within 51 days. Survival of F_1 fathead minnows was decreased in those exposed at

TABLE 6-1

Acute Lethal Effects of Captan to Freshwater Fish

Species	Duration (hr)	Concentration (mg/ℓ)	Method	Effect	Reference
Brook trout, *Salvelinus fontinalis*	96	0.034	constant-flow	LC_{50}	Hermanutz et al., 1973
Lake trout, *Salvelinus namaycush*	96	0.049	static	LC_{50}	Johnson and Finley, 1980
Goldfish, *Carassius auratus*	48	0.04	NR	LC_{50}	Spehar et al., 1982
Cutthroat trout, *Salmo clarkii*	96	0.056	NR	LC_{50}	Johnson and Finley, 1980
Chinook salmon, *Oncorhynchus tshawytscha*	96	0.057	constant-flow	LC_{50}	Johnson and Finley, 1980
Rainbow trout, *Salmo gairdneri*	96	0.073	constant-flow	LC_{50}	Johnson and Finley, 1980
Rainbow trout, *Salmo gairdneri*	72	0.32[a]	NR	LC_{50}	Anonymous, 1960
Channel catfish, *Ictalurus punctatus*	96	0.078	static	LC_{50}	Johnson and Finley, 1980
Brown trout, *Salmo trutta*	96	0.080	static	LC_{50}	Johnson and Finley, 1980
Yellow perch, *Perca flavescens*	96	0.120	static	LC_{50}	Johnson and Finley, 1980

TABLE 6-1 (cont.)

Species	Duration (hr)	Concentration (mg/ℓ)	Method	Effect	Reference
Coho salmon, Oncorhynchus kisutch	96	0.138	static	LC_{50}	Johnson and Finley, 1980
Bluegill sunfish, Lepomis macrochirus	96	0.072	contin-uous-flow	LC_{50}	Hermanutz et al., 1973
Bluegill sunfish, Lepomis macrochirus	96	0.141	contin-uous-flow	LC_{50}	Johnson and Finley, 1980
Fathead minnow, Pimephales promelas	96	0.065	constant-flow	LC_{50}	Hermanutz et al., 1973
Fathead minnow, Pimephales promelas	96	0.200	constant-flow	LC_{50}	Johnson and Finley, 1980
Carp, Cyprinus carpio	48	0.25	NR	LC_{50}	Spehar et al., 1982
Harlequin fish, Rasbora heteromorpha	48	0.33	constant-flow	LC_{50}	Tooby et al., 1975
Harlequin fish, Rasbora heteromorpha	96	0.30	constant-flow	LC_{50}	Tooby et al., 1975
Pond loach, Misgurnus anguillicaudatus	48	0.34	NR	LC_{50}	Spehar et al., 1982
Medaka, Oryzias latipes	48	1.00	NR	LC_{50}	Spehar et al., 1982

[a]Data reported for solution of orthocide 50-W, which is a compound containing 50% captan.

[b]50% mortality was reported for "larger" fish, while none died in a group of "smaller" fish.

NR = Not reported

0550p

08/28/84

0.0395 mg/ℓ. Growth of all minnows was significantly ($p<0.05$) reduced at 0.0395 mg captan/ℓ. Maximum acceptable toxicant concentrations (MATC) for the fathead minnow were therefore between 0.0165 and 0.0395 mg/ℓ. Based on chronic testing and MATC values for fathead minnows, MATC values for bluegill sunfish and brook trout were estimated to be 0.029-0.072 and 0.0075-0.018 mg captan/ℓ (Hermanutz et al., 1973).

Survival of zoeal stages of the Dungeness crab, Cancer magister, was not affected by 69 days of exposure at 0.030 mg captan/ℓ (Caldwell et al., 1978). Molting, however, was delayed in larval stages at 0.030 mg/ℓ. Survival of juvenile crabs was not affected at 0.290 mg/ℓ for 80 days or 0.510 mg/ℓ for 36 days. All adults exposed at 0.34 mg/ℓ survived for 75 days of exposure.

Brine shrimp, Artemia salina, eggs showed normal hatchability during exposure to 10 mg captan/ℓ (Kuwabara et al., 1980).

6.3. PLANT EFFECTS

After 30 days of exposure to captan at various concentrations, species of blue-green algae, including Nostoc sp., Calothrix sp., Westiellopsis prolifica, Aulosira fertilissima and Tolpothrix tenuis, tolerated levels as high as 500 mg/ℓ and showed growth (Babu and Bhalla, 1979). In the green algae, Chlorella vulgaris, 1 mg captan/ℓ reduced photosynthesis by 90%, and 10 mg/ℓ prevented the process completely (Malewicz and Borowski, 1979). At 0.1 and 1 mg captan/ℓ, growth of Dunaliella and Porphyridium sp. was slightly increased, but at 5 mg/ℓ growth was inhibited (Sikka and Butler, 1977). Growth of Skeletonema sp. was inhibited at 0.5 mg captan/ℓ.

6.4. RESIDUE

Hermanutz et al. (1973) reported that the half-life of captan in Lake Superior water at pH 6.5 and 23°C is ~8 hours. Colder water decreases its degradation, so that at 12°C a half-life of 40 hours was expected.

6.5. OTHER RELEVANT INFORMATION

Additional data pertinent to the effects of captan on aquatic organisms were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The U.S. EPA has established tolerances for captan residues in or on raw agricultural products (fruits and vegetables) at levels ranging from 0.25-100 ppm (Federal Register, 1980a). In addition, tolerances for transmission of captan residues to meat, milk and eggs from feeding captan-treated commodities or by-products to cattle or poultry have been set at 2-100 ppm for the designated commodities (e.g., almond hulls, beans) (Federal Register, 1980a). The FDA has approved the use of captan as a mold- and mildew-proofing agent in coatings for paper or paperboard products that contact food (Federal Register, 1980a).

In 1978, the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues established an ADI for captan of 0-0.1 mg/kg (IARC, 1983).

A TLV of 5 mg/m³ and a STEL of 15 mg/m³ for captan in workroom air have been recommended by the ACGIH (1980), based on the available toxicity data.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of captan were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

8. RISK ASSESSMENT

Only one positive carcinogenicity assay for captan in one strain of mice has been reported in the available published literature (NCI, 1977); however, there are positive mutagenicity and genotoxicity studies in bacterial systems in mammalian cell culture assays and in Drosophila (Clarke, 1971; Kada et al., 1974; Moriya et al., 1983; Wildeman and Nazar, 1982; Herbold and Buselmaier, 1976; Moriya et al., 1978; DeFlora and Boido, 1980; Shiau et al., 1981; Strobel and Greb, 1981; Bridges et al., 1972, 1973; O'Neill et al., 1981; Arlett et al., 1975; Tezuka et al., 1980; Vigfusson and Vyse, 1980; Waters et al., 1982). IARC (1983) has evaluated the data for the carcinogenicity of captan and concluded that results in mice (NCI, 1977) "provide limited evidence that captan is carcinogenic to experimental animals." In 1980, the U.S. EPA issued a Rebuttable Presumption Against Registration and continued registration of pesticide products containing captan, based on the conclusion that captan exceeds risk criteria for carcinogenicity and mutagenicity.

The data from the chronic oral study in male B6C3F1 mice (NCI, 1977) were, therefore, used to estimate a cancer risk level. Assuming that a mouse consumes the equivalent of 13% of its body weight/day as food, the average doses corresponding to 8000 and 16,000 ppm in the diet were 1040 and 2080 mg/kg/day. Using the occurrence of polypoid carcinoma (i.e., adenocarcinoma in adenomatous polyp) combined with adenomatous polyp (not otherwise specified) and the linearized multi-stage model adopted by the U.S. EPA (Federal Register, 1980b), a carcinogenic potency factor (q_1^*) of 2.336×10^{-3} $(mg/kg/day)^{-1}$ can be derived for humans. The conversion factor used in the calculation of q_1^* values for humans (assuming 70 kg bw) from animal data is the cube root of the body weight ratio (Federal

Register, 1980b). The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 4.23×10^{-3} mg/kg/day, or 2.96×10^{-1} mg/day for a 70 kg man. Data used in the derivation of the q_1^* are presented in Appendix B.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can be presented in this chapter.

The CBI Appendix to this document reviews other animal studies that provide further evidence that captan is carcinogenic to mice. A more conservative q_1^* of 1.01×10^{-2} $(mg/kg/day)^{-1}$, calculated from dose-response data for duodenal adenomas and adenocarcinomas in female mice fed captan in the diet, is recommended for use in estimating the increased risk of cancer that is due to captan exposure.

The CBI data on the carcinogenicity of captan are currently being evaluated by the Office of Pesticide Programs and are scheduled for inclusion in a forthcoming position document. When these data are available, they will be reviewed by the Carcinogen Assessment Group (CAG) and this review will be reflected in an updated draft of this document.

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APPENDIX A

Literature Searched

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

Most of these searches were conducted in July, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound:	Captan
Reference:	NCI, 1977
Species, Strain, Sex:	Mouse, B6C3F1, Male
Body Weight:	0.028 kg (average measured)
Length of Exposure (l_e):	560 days
Length of Experiment (L_e):	637 days
Lifespan of Animal (L):	730 days
Tumor Site and Type:	Duodenum, adenocarcinomas in adenomatous polyp and adenomatous polyp (not otherwise specified)
Route, Vehicle:	Oral, feed

Experimental Dose or Exposures mg/kg/day	Transformed Dose mg/kg/day	Incidence No. Responding/No. Tested (or Examined)
0	0	0/68
1040	914.3	3/43
2080	1829	5/46

Human $q_1^* = 2.336 \times 10^{-3}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 4.23×10^{-3} mg/kg/day or 2.96×10^{-1} mg/day for 70 kg human